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Beneficial effect of renal transplantation on cognitive brain function

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Beneficial effect of renal transplantation on cognitive brain function. Cognitive brain dysfunction is a common complication of end-stage renal disease. To investigate the cerebral effect of renal transplantation, we studied P300 event-related potentials—an objective marker of cognitive brain function—trailmaking test and Mini-mental state in 15 chronic hemodialysis patients and 45 matched healthy subjects. Before transplantation, patients showed prolonged P300 latency (364 vs. 337 ms, $P < 0.01$), smaller amplitude (15.2 vs. 19.1 μV) and scored lower ($P < 0.05$) in trailmaking test and Mini-mental state as compared to healthy subjects. Following renal transplantation (14 months), P300 latency decreased (337 ms, $P < 0.01$ vs. before) and amplitude increased (17.4 μV, $P < 0.05$ vs. before), indicating improved cognitive brain function. The trailmaking test and Mini-mental state tended to improve. Following transplantation, P300 findings, trailmaking test and Mini-mental state were not different from healthy subjects. Additional studies following erythropoietin treatment in 6 of the 15 hemodialysis patients revealed decreased (improved) P300 latency (351 vs. 379 ms before, $P < 0.05$) with further decrease following transplantation (341 ms, $P = 0.06$). Our findings indicate that cognitive brain dysfunction in hemodialysis patients may be fully reversed by successful renal transplantion.

Nervous system dysfunction is a major complication of end-stage renal disease [1, 2]. Uremic encephalopathy as a part of the uremic syndrome encompasses a wide spectrum of neurobehavioral and neurological disturbances ranging from fatigue, slowing and intellectual impairment to dementia, seizures, delirium and coma [3–5]. Although severe neurological symptoms are partially or completely reversed by adequate hemodialysis, even optimally dialyzed patients will usually not return to normal neurocognitive function. Moreover, dialysis therapy itself may be associated with distinct neurological disturbances [4, 6]. Patients on hemodialysis perform poorly in various cognitive tasks [3, 4, 7, 8].

The pathophysiology of cognitive dysfunction has not been clarified yet. Plasma levels of uremic solutes, parathormone and aluminium correlate not or inconsistently with the degree of brain dysfunction [9–12]. Since substantial cognitive and electrophysiological improvements were observed following recombinant human erythropoietin (rHuEPO) treatment, severe anemia of chronic renal failure has been shown to be directly associated with cognitive dysfunction, reduced working capacity and impaired well-being [7, 13–18]. Anemia, however, is alleviated but not fully abolished with rHuEPO at the commonly recommended dosage; other metabolic disturbances of uremia are unchanged or may be worsened secondary to increased appetite and reduced dialyzer clearance of small solutes [19]. Elevated plasma levels of neuroinhibitory peptides are not corrected by rHuEPO treatment [20].

Renal transplantation usually restores erythropoietin production and corrects anemia [21]. Renal excretory, metabolic and endocrine function are recovered, nutritional state is improved [22]. Daily performance and quality of life are improved following transplantation [23–26]. A beneficial effect on cognitive performance is clinically evident, but objective data are lacking [27–29]. The present study was designed to objectively evaluate the impact of successful renal transplantation on cognitive brain function by using P300 cognitive evoked potentials and psychometric tests.

Evoked potentials, stable electrical brain sequences following a stimulus, have been demonstrated to sensitively assess cerebral functional state in various neurological and metabolic diseases [30–33]. P300 event-related potentials are late positive cortical deflections occurring after certain cognitive tasks (Fig. 1). They objectively reflect important aspects of neurocognitive function. P300 latency is thought to be related to signal-processing speed and stimulus evaluation time, P300 amplitude varies with the amount of conscious attention paid to a stimulus [34]. Subclinical brain dysfunction is more sensitively and objectively detected by P300 latency than by EEG and psychometric tests [35, 36]. P300 peak latency is delayed with aging [37], in dementia [38], schizophrenia [39], focal brain lesions [40], multiple sclerosis [41], carotid artery stenosis [42], hepatic encephalopathy [35] and chronic renal failure [8, 9, 14]. As our group and others have previously shown, P300 latency is decreased and amplitude is increased following rHuEPO treatment in hemodialysis patients [13–16, 43].

Patients

Fifteen patients (age 45 ± 13 years, 7 male, 8 female) were studied 12 to 24 hours after maintenance bicarbonate hemodialysis and, on a second occasion, 14 ± 5 months after successful cadaveric ($N = 14$) or living-related-donor ($N = 1$) renal transplantation, 36 ± 21 months after initial study. Informed consent was obtained from all patients and the study was approved by institutional review. Underlying renal disease was glomerulonephritis in eight, pyelonephritis in four, interstitial nephropathy in

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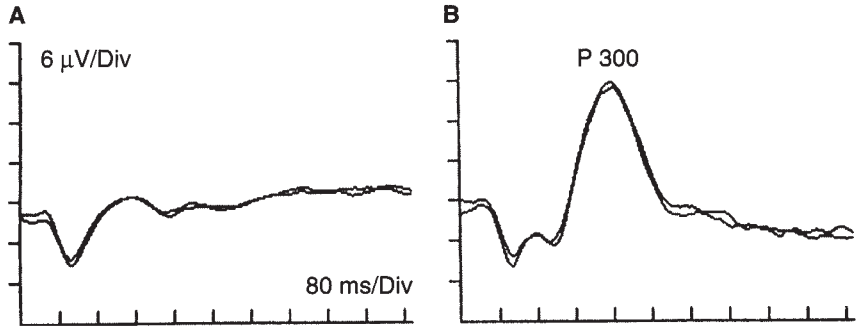

Fig. 1. *P300 waveforms obtained at Cz (grand average of two repeated tasks) in 25 normal healthy subjects.* (**A**) Responses to frequent background tones (80%, 1000 Hz). (**B**) P300 event-related responses to rare target tones (20%, 2000 Hz).

two and polycystic kidney disease in one patient. Dialysis was prescribed to a delivered Kt/V > 1.2 in four-hour dialysis sessions thrice weekly. Dialyzer membrane material was polysulfone in 11 and cellulose acetate in 4 patients. Median dialytic age was 16 months (range, 3 months to 8 years). In 10 patients before and in 11 patients after renal transplantation, there was a history of hypertension which was well controlled by antihypertensive agents. Six patients (3 males, 3 females, 51 ± 14 years) were started on rHuEPO treatment after initial measurement (rHuEPO, Boehringer Mannheim, Indianapolis, IN, USA; 4330 ± 820 units i.v. thrice weekly) and underwent additional evaluation four months after initiating rHuEPO. Maintenance immunosuppression after transplantation was cyclosporine and prednisolone in 10 and additional azathioprine in 5 patients. One patient received additional cyclophosphamide and regular immunoapheresis for controlling polyreactive HLA-antibodies. Only stable non-demented outpatients (Mini-mental state score of ≥ 24) without any evidence of neurological, infectious, vascular or immunological complications were eligible for the study. Systemic disorders like diabetes, amyloidosis, malignant hypertension and multiple myeloma were excluded. Sedatives were withdrawn at least one week prior to evoked potential recording. Forty-five sex- and age-matched controls were elected from a group of 169 apparently healthy volunteers. To evaluate the influence of hemoglobin on cognitive brain function, we studied 6 additional hemodialysis patients with normal hemoglobin levels (3 males, 3 females, 46 ± 14 years; hemoglobin 13.3 ± 1 g/dl) and 6 severely anemic patients with chronic gastrointestinal blood loss and normal renal function (2 males, 4 females, 47 ± 16 years; hemoglobin 6.6 ± 1.3 g/dl; Crohn's disease in 3, gastric ulcer in 2 and ulcerative colitis in 1 patient). Further, 5 patients following transplantation with allograft rejection or chronic cyclosporine nephrotoxicity (47 ± 6 years) were studied (Table 3).

Methods

Evoked potentials

Evoked potentials were recorded under comparable conditions on a Nicolet CA 2000 electrodiagnostic system (Nicolet, Madison, WI, USA) with Ag/AgCl-sinter electrodes (Picker Int., Munich, Germany) and adhesive electrolyte gel (Grass, Quincy, MA, USA). Active electrodes were placed at Cz (vertex) and Fz (frontal) according to the International 10/20 System [44] and referenced to linked earlobes, C3 being common electrode. Impedance was maintained below 3 kiloohms, filter bandpass was 0.01 to 30 Hz in order to avoid distortion [34]. The auditory oddball paradigm consisted of randomly intermixed background (80%, 1000 Hz) and target (20%, 2000 Hz) pips tones binaurally delivered by headphones at 55 dB nHL. Patients and controls were seated comfortably and were instructed to keep a running mental count of target tones. EEG epoques of 800 ms after each tone were amplified and averaged separately (Fig. 1), responses contaminated with muscle or eye movement artifacts were rejected. At least 25 EEG epoques following the target tones were averaged; the task was repeated to confirm reproducibility. Attention was verified by comparing actual stimulus number with number counted by the patients. In case of a > 10% discrepancy, the trace was rejected. A large positive deflection later than 280 ms was defined as P300 [34]. Peak latencies were obtained by extrapolation of adjacent slopes [38] and reviewed by a second physician. Amplitudes were calculated between P300 and N400 peaks according to standard methods [34].

Psychometric tests

Trailmaking test A [45] and Mini-mental state [46] were performed in order to assess cognitive and psychomotor function and exclude demented subjects. At different occasions, we used different trailmaking tables to minimize learning effect.

Statistics

Data are expressed as means ± SD. Calculations were performed with the statistical software package SAS® (SAS Institute Inc., Cary, NC, USA), P values of less than 0.05 (two-tailed test) were considered statistically significant. Data were checked for normality using the Wilk-Shapiro test. Results obtained at baseline, after rHuEPO and following transplantation were compared with paired Student's t-test or Wilcoxon test for paired data. Comparison between patients and controls was performed with either analysis of variance or Wilcoxon two-sample procedures. The impact of certain clinical and laboratory data on evoked potential and psychometric findings was investigated with Pearson and Spearman correlation coefficients and linear regression analysis.

Results

Laboratory data

Laboratory data are represented in Table 1. After transplantation, abnormal levels of azotemia fell significantly ($P < 0.001$ vs. hemodialysis) but did not reach the normal range. Hemoglobin values showed a significant increase reaching the normal range in 11 and remaining below the lower normal limit of 12 g/dl in 4 patients. In a subgroup of 6 patients, hemoglobin increased from

Table 1. Laboratory data in hemodialysis patients (predialytic values) before and following renal transplantation and in matched healthy subjects (standard values from our laboratory)

	Hemodialysis Transplantation ($N = 15$)		Healthy subjects ($N = 45$)
Hemoglobin *g/dl*	7.5 ± 1.1[a]	13.3 ± 2.1[a,b]	14.7 ± 1.5
Hematocrit *%*	23.3 ± 3.2[a]	40.7 ± 7.4[a,b]	46 ± 4
Creatinine *mg/dl*	10.7 ± 3.0[a]	1.5 ± 0.5[a,b]	1.0 ± 0.1
Blood urea nitrogen *mg/dl*	75 ± 16[a]	25 ± 9[a,b]	17 ± 4

[a] $P < 0.01$ vs. healthy subjects
[b] $P < 0.01$ vs. hemodialysis

Table 2. P300 measurements and psychometric tests in 15 hemodialysis patients before and following renal transplantation and in 45 matched healthy subjects

	Hemodialysis Transplantation ($N = 15$)		Healthy subjects ($N = 45$)
Age *years*	44 ± 14	46 ± 14[a]	44 ± 16
P300 latency *Cz, ms*	364 ± 34[b]	337 ± 25[a]	337 ± 22
P300 latency *Fz, ms*	362 ± 34[b]	337 ± 22[a]	334 ± 21
P300 amplitude *Cz, μV*	15.2 ± 5.6	17.4 ± 4.3[c]	19.1 ± 7.6
P300 amplitude *Fz, μV*	14.9 ± 4.9[d]	17.4 ± 4.2[c]	19.1 ± 7.5
Trailmaking test A *seconds*	34 ± 10[d]	29 ± 8	28 ± 9
Mini-mental state	28.5 ± 2.0[b]	29.1 ± 0.9	29.5 ± 0.8

[a] $P < 0.01$ vs. hemodialysis; [b] $P < 0.01$ vs. healthy subjects; [c] $P < 0.05$ vs. hemodialysis; [d] $P < 0.05$ vs. healthy subjects.

7.0 ± 0.4 to 9.2 ± 1.1 g/dl following rHuEPO treatment ($P < 0.01$) and to 11.7 ± 1.3 g/dl following transplantation ($P < 0.01$).

Evoked potentials

P300 results are represented in Table 2 and Figure 2. When compared to matched healthy subjects, P300 latencies at Cz and Fz were delayed ($P < 0.01$) and amplitudes were smaller ($P < 0.05$) before but not following transplantation. Following transplantation, P300 latencies at Cz and Fz decreased ($P < 0.01$ vs. hemodialysis) and amplitude increased ($P < 0.05$) both indicating improved cognitive brain function. In a subgroup of 6 patients (51 ± 14 years), P300 latency was significantly reduced following rHuEPO treatment (351 ± 26 after vs. 379 ± 17 ms before, Cz, $P < 0.05$). Further improvement was observed following transplantation (341 ± 25 ms, Cz, $P = 0.06$). P300 amplitude at Cz (19.8 ± 7.3 μV following rHuEPO vs. 17.7 ± 5.3 μV before) and following transplantation (18.6 ± 2.7 μV) did not yield statistical significance. Similar results were obtained at Fz (data not shown). P300 latency in 6 hemodialysis patients with normal hemoglobin (13.3 ± 0.4 g/dl) was 355 ± 19 ms, amplitude was 12.3 ± 8.0 μV. In contrast, patients with chronic gastrointestinal blood loss (hemoglobin 6.6 ± 1.3 g/dl) performed better in P300 (peak latency at Cz 343 ± 14 ms; amplitude 17.9 ± 3.8 μV). Patients with graft rejection and cyclosporine nephrotoxicity are represented in Table 3. Graft dysfunction was associated with neurocognitive dysfunction in all cases.

Psychometric tests

Psychometric results are represented in Table 2. When compared to healthy subjects, patients scored lower in the Mini-mental state and trailmaking test while on hemodialysis ($P < 0.05$) but not following transplantation. Improvement following transplantation as well as changes following rHuEPO treatment in a subgroup of 6 patients (data not shown) failed to reach statistical significance. Mini-mental state and trailmaking test did not discriminate between uremic patients with normal hemoglobin and patients with normal renal function and low hemoglobin (Mini-mental state 29.5 ± 0.8 vs. 29.2 ± 1.2; trailmaking 40 ± 17 vs. 34 ± 14 seconds, respectively).

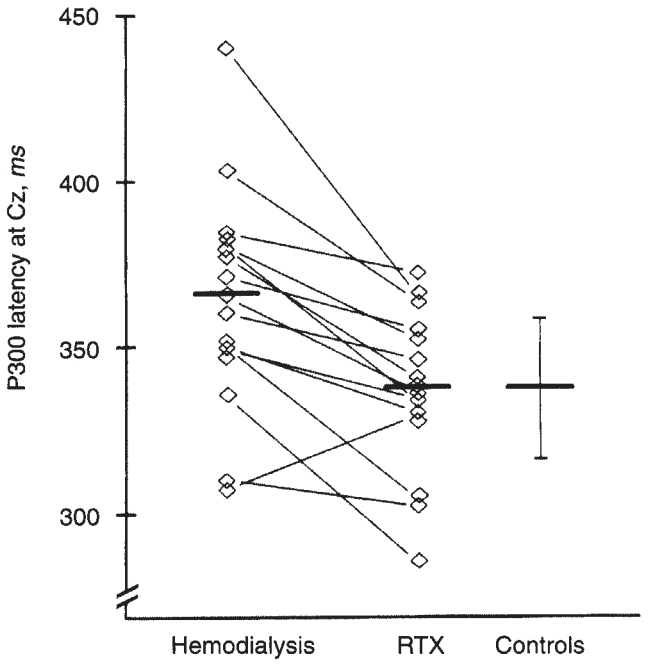

Fig. 2. *P300 peak latencies referenced at CZ in 15 patients before and after renal transplantation (RTX) compared with 45 matched healthy subjects.*

Correlations

The influence of age, dialytic age, hemoglobin, hematocrit, blood urea nitrogen, creatinine, sodium and potassium on N100, P200, P300 and N400 latencies and amplitudes at Cz and Fz, Mini-mental state and trailmaking test before and following transplantation was tested by Pearson and Spearman correlation and linear regression analysis (Table 4). Before transplantation, significant correlations with P300 latency were obtained for age, hemoglobin, hematocrit and erythrocytes. After transplantation, age was the only parameter correlated to P300 latency which was the case in healthy control subjects (Table 4). All other tested correlations did not reach statistical significance.

Discussion

Our data unequivocally demonstrate that cognitive brain function is improved in chronic hemodialysis patients following successful renal transplantation. Cognitive P300 findings following transplantation equaled those of healthy subjects indicating that uremic encephalopathy may be fully reversible. Frontal and central leads were equally affected indicating widespread cerebral benefit not restricted to particular areas.

In spite of various psychological and neurophysiological studies in terminal renal failure and considerable research work on

Table 3. P300 measurements (CZ) and psychometric tests in patients with graft rejection and cyclosporine nephrotoxicity

Initials	Age	Diagnosis	Hemoglobin *g/dl*	Creatinine *mg/dl*	P300 latency *Cz, ms*	P300 amplitude *Cz, μV*	Trailmaking tests *seconds*	Mini-mental state
M.E.	54	acute graft rejection	14.4	3.7	448	5.4	—	28
D.E.	37	chronic graft rejection	8.0	2.7	350	7.3	40	30
H.S.	49	chronic graft rejection	8.7	4.1	362	12.7	36	30
J.R.	46	chronic CsA toxicity	7.5	2.5	358	7.3	55	28
S.M.	49	chronic CsA toxicity	10.2	3.0	380	25.6	65	30

Abbreviation CsA is cyclosporine A.

Table 4. Correlations and linear regression analysis

	Correlation	Regression	*P*
Influence of age (x) on P300 latency at Cz (y)			
Hemodialysis	r = 0.74	y = 293 + 1.59x	< 0.01
Transplantation	r = 0.70	y = 279 + 1.25x	< 0.01
Healthy subjects	r = 0.67	y = 296 + 0.93x	< 0.001
Influence of hemoglobin (x) on P300 latency at Cz (y)			
Hemodialysis	r = 0.58	y = 501 − 18.5x	< 0.05
Transplantation	r = −0.38	y = 277 + 2.07x	NS

cognitive effects of rHuEPO therapy [6–16], there are no reliable data on cognitive brain function following renal transplantation. Improvement of peripheral nerve conduction is well-known following transplantation [29, 47]. Somatosensory potentials, reflecting afferent neural transmission, were improved secondary to enhanced peripheral but not central signal conduction [29]. Visual evoked potentials (VEPs), usually delayed in renal failure [9, 10], yielded conflicting results. Kuba et al reported prolonged VEP latencies and larger amplitudes in transplant recipients when compared to a normal collective [28]. Yu and colleagues found increased (worsened) latencies and increased (improved) amplitudes when compared to pretransplantation values [29]. Brown, Sufit and Sollinger reported reduced (improved) latencies following transplantation; amplitudes were reduced (impaired) in nondiabetic and increased in diabetic subjects [27]. Although these data may reflect functional alterations of visual pathways, they do not indicate any impact of renal transplantation on cognitive brain function. Contrasting to P300, VEP N100 latency is not known to correlate with cognitive performance. VEPs were not a reliable tool for the diagnosis of hepatic encephalopathy in the individual patient [48]. We have demonstrated that VEPs were not capable to detect improvement of cognitive brain function following rHuEPO in uremic encephalopathy [13]. In contrast, P300 potentials provided high sensitivity in detecting overt and subclinical brain dysfunction, as demonstrated in evaluating rHuEPO treatment and hepatic encephalopathy [13–16, 35]. Low intraindividual P300 latency test-retest variability (reflected by a mean variation coefficient of 0.8% in uremic and 2% in normal subjects) confirmed excellent reproducibility [13].

Although P300 potentials represent a well-established measure of cognitive brain function, they have not yet been employed to evaluate cognitive effects associated with renal transplantation. We found that P300 latency decreased (improved) from 364 to 337 ms ($P < 0.01$) and P300 amplitude increased (improved) from 15.2 to 17.4 μV ($P < 0.05$) indicating significant mental improvement following transplantation. As cognition influences personal, social and vocational activity, our results may, beside other factors, explain the reported amelioration of subjective quality of life and the sense of well-being and life satisfaction following renal transplantation [23–26]. Improved cognitive brain function may be directly related to improved quality of life defined as functioning interactions between individual and environment [26].

Psychometric tests have been frequently employed in renal failure [3, 14, 46]. In this setting, we used the Mini-mental state (a bedside evaluation of cognitive function within 10 min) primarily as a screening test for exclusion of demented subjects [46]. A trend towards improvement was observed following transplantation (29.1 vs. 28.5). Trailmaking test tended to improve (29 vs. 34 s) indicating improved psychomotoric performance following transplantation. Psychometric improvement, however, did not yield statistical significance probably due to a lower sensitivity as compared to P300 [13]. It is conceivable that more sensitive neuropsychological methods would have demonstrated more distinct changes. However, since even those time-consuming test batteries are not without methodological bias [49], emphasis was layed on the P300 method.

Pathophysiological mechanisms of uremic encephalopathy are controversely discussed [4]. Commonly measured blood parameters such as creatinine, blood urea nitrogen, phosphate, pH and bicarbonate failed to correlate with clinical and neurophysiological data [9, 11–13]. No significant correlation between electrophysiological data and biochemical blood parameters was detected in our patients. Hyperparathyroidism possibly accounts for impaired nerve conduction velocity but did not correlate with cognitive dysfunction and evoked potential findings [9, 11, 12]. Since rHuEPO treatment has been convincingly demonstrated to improve various measures of cognitive performance in hemodialysis patients, severe anemia due to erythropoietin deficiency is now considered a pivotal cause of cognitive impairment [13–16, 50]. Accordingly, the low initial hemoglobin of 7.5 g/dl influenced cognitive brain function as expressed by a significant negative correlation of hemoglobin and P300 latencies prior to transplantation in this study (Table 4). Comparable to rHuEPO treatment in our previous report [13], correction of severe anemia following renal transplantation cancelled P300 correlation with hemoglobin in this study. Following transplantation, age was the only variable correlated to P300 latency, as it was the case in normal subjects and is known from the literature [34, 37]. Hence, cognitive brain function was negatively affected by severe but not by moderate anemia. In the higher range of hemoglobin, no correlation to cognitive brain function was observed and it has not been

described in the literature. Pathophysiologically, increase in hemoglobin to normal or near-normal values with subsequent increase of cerebral oxygen delivery may account for the beneficial cerebral effect of transplantation. However, as cerebral oxygen consumption measured by positron emission tomography was markedly depressed in hemodialysis patients before and after rHuEPO treatment, and patients with severe anemia due to gastrointestinal blood loos had better cognitive function than hemodialysis patients with twice as high hemoglobin levels, anemia cannot be the only contributor to uremic brain dysfunction [51]. Accordingly, neither partial or full anemia correction with rHuEPO [13, 16] did completely normalize brain function in hemodialysis patients. Additional metabolic and/or neuroendocrine factors related to uremia have to be considered in the pathophysiology of uremic brain dysfunction [4]. Whether the striking reduction of small and middle molecular weight solutes, the absence of periodic fluid and electrolyte shifts associated with hemodialysis or other factors such as increased utilization of adenosine triphosphate (ATP) or decreased cerebral blood flow may contribute to improved cerebral performance remains speculative [4, 14, 51]. Since anemia and metabolic factors are largely corrected by successful renal transplantation, the beneficial cerebral effect of transplantation exceeded that of rHuEPO in the current study. However, we could also demonstrate that graft dysfunction was associated with considerable brain dysfunction.

In summary, cognitive brain function measured by P300 evoked potentials and psychometric tests is improved in hemodialysis patients following successful renal transplantation. Uremic encephalopathy may be fully reversible even after years on hemodialysis. This result in spite of increased risk of hypertension, cerebrovascular events, opportunistic CNS infections and cyclosporine neurotoxicity following transplantation is remarkable [52–55]. Improvement of cognitive brain function in hemodialysis patients following successful renal transplantation strongly endorses transplantation as optimal therapy for chronic renal failure.

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